REMARKS

The claims have been amended to further define the invention. The isolated chamber of the instrument has a volume of less than 1.2 cubic millimeters, and a plurality of miniature biopsy sampling devices are included on a single catheter, e.g., 10, 20, 50, and up to hundreds of miniature sampling devices. In contrast to the cited prior art, the claimed method permits minimally invasive diagnostic procedures using picoliter to microliter volumes.

Claims 1-23 and 26-30 are pending. New claims 27-30 have been added; these claims are supported by disclosure at page 2, lines 12-15, and on page 5, lines 8-13, of the specification.

The Examiner has called attention to the term "abstracting" at page 3, line 20, of the specification and has requested rectification of an apparent typographical error. The entire sentence reads, "Also within the invention is a plurality of tissue sampling devices positioned on a catheter or needle for abstracting at least one tissue sample from a living subject." In this context, the word means to take away or remove (see Attachment A, dictionary definition for abstract). Accordingly, Applicants believe that correction is not required.

The drawings were objected to, because the lines were not of uniform thickness. To address the informality of the drawings, Applicants submit herewith formal drawings

No new matter has been added by this amendment.

35 U.S.C. 102

Claims 1-6, 8, 10, 12 and 17-19 were rejected for anticipation by Mosse et al., (WO 00/44285). Claims 1 and 17 have been amended to require that the volume of the isolated chamber be less than 1.2 millimeters. Mosse et al. fail to describe a chamber with the volume requirements of the amended claims. Withdrawal of this rejection is therefore requested.

35 U.S.C. 103

Claim 16 was rejected for obviousness over Mosse et al. The Examiner states:

> Mosse does not expressly disclose that the volume of the isolated chamber ranges from 0.001 to 1 cubic millimeter. At the time the invention was made, it would have been an obvious matter of design choice to a person of ordinary skill in the art to make the volume of the chambers between 0.001 and 1 cubic millimeter because Applicant has not disclosed that this range of volumes provides an advantage, is used for a particular purpose, or solves a stated problem. One of ordinary skill in the art, furthermore, would have expected Applicant's invention to perform equally well with a different chamber volume because the instrument would still successfully obtain biopsy samples. Therefore, it would have been an obvious matter of design choice to modify Mosse to obtain the invention as specified in claim 16.

The device of Mosse et al. is an endoscope for taking multiple biopsies from the oesophagus in an oriented fashion (page 2, lines 13-18, of Mosse). As is well known in the art, an endoscope is a device used for examining visually the interior of a bodily canal or a hollow organ such as the esophagus, colon, bladder, or stomach. In this case, the endoscope is equipped with recesses for holding biopsies for the purpose of determining gross pathology of the margins of a precancerous/cancerous state known as Barrett's esophagus.

> Segments of Barrett's esophagus may extend 3 to 10 centimetres or more above the gastroesophageal junction. Segments of Barrett's eosophagus shorter than 3 cms used to be regarded as a normal finding at endoscopy but probably also have a risk of progression to cancer. It has been recommended that biopsies are taken from four quadrants of Barrett's oesophagus at either 1 or 2 centimetre intervals al alternate years for histological assessment to look for changes such as dysplasia which may predict or indicate the development of cancer. (page 1 of Mosse et al.)

Consistent with the use of Mosse's device, the reference states that the openings are somewhat smaller than the recesses, being typically 3 to 5 mm in diameter (page 5, lines 19-20 and Figs. 2a, 2b). Mosse et al. further state that a piece of tissue (mucosa and submucosa) nearest the surface of the oesophagus is drawn in. The recesses are made sufficiently shallow that deep muscle tissue is not drawn in (page 6, lines 18-20, of Mosse). The depth of the mucosal and submucosal tissue drawn in is on the order of millimeters (e.g., 3 mm; Lim et al, 1999, Dig. Dis. 17:145-152; Attachment B). Thus, the volume of the chambers is approximately an order of magnitude different from that of the claimed invention. (e.g., less than 1.2 cubic millimeters, 0.001 to 1 cubic millimeter).

The invention utilizes miniature biopsy sampling devices consistent with the goal of accomplishing a diagnosis in a minimally invasive manner. Unlike Mosse's device, which is used to map gross anatomical changes, the claimed sampling method interfaces with analytical tests that use a minimal amount of tissue per analytical procedure. The method of the invention provides distinct advantages as taught in the specification (page 5, lines 23-29).

> For example, the analysis and examination of smaller tissue and/or fluid samples reduce the amount of tissue required per analytical procedure. Analytic methods, e.g., Polymerase Chain Reaction (PCR), are used to obtain diagnostic information. The instrumentation and sampling methods described herein permit the replication of genetic data from very small samples, eliminating the need for large tissue samples.

It would not have been obvious to modify Mosse's endoscope as now claimed, because the cited prior art does not describe the microminiaturization of sampling and analysis approach taught and claimed by the Applicant. In view of the claim amendments, clarifications provided above, and stated advantages of the claimed instrument, Applicants submit that claim 16 is nonobvious over the prior art. The remaining claims contain similar volume requirements and are nonobvious over Mosse et al. for the same reasons.

Claims 7, 20-23, and 26 were rejected for obviousness over Mosse et al. in view of Sorenson et al. (U.S. Patent No. 5,320,627). These claims require a heating element for actuating a mechanical portion of the sampling device to collect and retain a sample. The Examiner stated:

> it would have been obvious to one having ordinary skill in the art at the time of invention to have used a heating element for causing actuation of a mechanical portion to collect and retain a biopsy sample as taught by Sorensen in place of the mechanical actuation of Mosse in order to achieve the predictable result of actuating a biopsy mechanism to obtain biopsy sample.

Sorenson merely describes a heating element and provides no addition description regarding the other novel and nonobvious elements of the invention as now claimed. As discussed above, the claims have been amended to clarify the size of the isolated tissue sample chamber and the method of obtaining numerous miniature tissue samples in a minimally invasive manner, thereby avoiding pain and trauma associated with removal of large tissue samples for diagnostic procedures. Applicants submit that these profound advantages are sufficient to overcome the articulated obviousness rejections and respectfully request withdrawal of these rejections.

CONCLUSION

Applicant believes the amended claims are in condition for allowance, which action is respectfully requested. Applicant reserves the right to prosecute claims which are equal to or broader in scope in this or future applications related to the above-identified patent application.

Should the Examiner have any questions concerning the enclosure submitted herewith, the Examiner is invited to telephone the undersigned agent of record at the number provided.

The Commissioner is hereby authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311 (Reference No. 26859-002).

Respectfully submitted,

Ingrid A. Beattie, Reg. No. 42,306
Attorney(s) for Applicant
c/o MINTZ, LEVIN
Address all written correspondence to
Customer no.: 30623
Tel: (617) 542-6000
Fax: (617) 542-2241

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to pull, draw — more at TRACE] **1** *archaic* : absent in mind : ABSTRACTED 3 〈~, as in a trance —John Milton〉 **2** [ML *abstraetus*, fr. L, past part.] **a** : considered apart from any application to a particular object or specific instance : separated from embodiment 〈an ~ entity〉 〈arguments from ~ probability —P.E.More〉 **b** : difficult to understand : ABSTRUSE 〈more ~ problems involving judgment and ability to reason —*Saturday Rev.*〉 **c** : IDEAL 〈to shed tears over ~ justice and generosity . . . and never to know these qualities when you meet them in the street —William James〉 **d** : insufficiently factual : FORMAL 〈she possessed all civil rights — but these were ~ and empty —H.M.Parshley〉 〈~ and doctrinaire instruction〉 **e** *of a unit or number* : having no reference to a thing or things — opposed to *concrete* **3** *archaic* : drawn away : REMOVED, SEPARATE **4** : expressing a property, quality, attribute, or relation viewed apart from the other characteristics inhering in or constituting an object 〈*honesty, whiteness, triangularity* are ~ words〉 **5** : dealing or tending to deal with a subject in the abstract: as **a** *of a science* : PURE, THEORETICAL — contrasted with *applied* **b** : IMPERSONAL, DETACHED 〈I should have remained mainly academic and ~ but for the war —Bertrand Russell〉 〈the ~ compassion of a surgeon —*Time*〉 **6 a** *of a fine art* : presenting or possessing schematic or generalized form frequently suggested by and having obscure resemblance to natural appearances through a contrived ordering of pictorial or sculptural elements — contrasted with *academic;* compare NONOBJECTIVE **b** *music* : ABSOLUTE 11a **c** *of dance composition* : lacking concrete program or story **7** : signifying a logical predicate or a class esp. of higher order (as number when conceived of as a class property)

²ab·stract \ˈ" *in sense 2; in other senses usu* ˈ•,•\ *n* -s [ME, fr. L *abstractus*, past part.] **1** : a summary or an epitome (as of a book, a scientific article, or a legal document) **2** : an abstract term or idea : the result of abstraction **3** : something that comprises or concentrates in itself the essential qualities of a larger thing or of several things 〈a man who is the ~ of all faults that all men follow —Shak.〉 〈trial by jury . . . the very ~ and essence of . . . democratic government —W.H. Mallock〉 **4** : ABSTRACT OF TITLE **5** *pharmacy* : a preparation made by mixing a powdered solid extract of a vegetable substance with sugar of milk in such proportion that one part of the final product represents two parts of the original drug from which the extract was made **6** *fine art* : ABSTRACTION 6 **syn** see ABRIDGMENT — **in the abstract** : with reference to theoretical considerations only : apart from practical or actual conditions

³ab·stract *in vt senses 3 & 6 usu* ˈ•,•\; *in other senses usu like adj*\ *vb* -ED/-ING/-S [*¹abstract*] *vt* **1** : to draw away : take away : REMOVE, SEPARATE 〈add or ~ baser metal in minting〉 〈a vast cigar-shaped body of gas was raised and eventually *~ed* from the surface of the sun —W.E.Swinton〉 **2** : to separate (as an idea) by the operation of the mind : consider (as a quality or attribute) apart from any application to a particular object or instance 〈~ the notion of dimension from that of space〉 **3** : to make an abstract of : EPITOMIZE, SUMMARIZE **4** : to draw away the interest or attention of : DIVERT 〈his imagination had so *~ed* him that his name was called twice before he answered —James Joyce〉 **5** : to take secretly or dishonestly : STEAL, PURLOIN 〈Shaftesbury's son seems to have *~ed* important documents for Cavour —*Times Lit. Supp.*〉 **6** *in life insurance* : to summarize (an insurance contract) esp. in the effort to induce a policyholder to cancel a policy and substitute another **7** *fine art* : to create abstractions suggested by (a concrete or natural object) 〈~ *vi* **1** : to perform the process of abstraction or of abstracting something 〈we naturally ~ when two similar objects are presented to us —Frank Thilly〉 **2** *fine art* : to create abstractions **syn** see DETACH — **abstract from** : to leave out of consideration

abstracta *pl of* **abstractum**

ab·stract·ed \(ˈ)•ˈ•,•\ *adj* **1** *archaic* : ABSTRACT 2 **2** : drawn away : REMOVED, SEPARATE, APART 〈the evil one ~ stood from his own evil —John Milton〉 〈possibility is that in which stands achievability, ~ from achievement —A.N.Whitehead〉 **3** : withdrawn in mind : inattentive to surrounding objects : PREOCCUPIED, ABSENTMINDED 〈sitting silent and ~〉 〈their pallid ~ air of human beings devoted to a difficult ideal —Herman Wouk〉 — **ab·stract·ed·ly** *adv* — **ab·stract·ed·ness** *n* -ES

abstracter *var of* ABSTRACTOR

abstract expressionism *n* : the theory or practice of freely creating (as in painting) abstractions characterized by sinuous linearity, organic shape, and highly decorative surface

ab·strac·tion \abzˈtrakshən, əb-, -bˈst-\ *n* -S [ME or ML; MF, fr. ML *abstraction-, abstractio*, fr. LL, abduction, fr. L *abstractus* (past part. of *abstrahere* to draw away, withdraw) + *-ion-, -io* -ion — more at ABSTRACT] **1** : the act of drawing or taking away : the state of being drawn or taken away : REMOVAL, SEPARATION 〈labels bearing a clearly printed notice of addition or ~〉 〈in search of seclusion, of loneliness, of . . . ~ from the trivial round —*Times Lit. Supp.*〉 〈suspected of the ~ of money from the mail〉 **2 a** : the act or process of leaving out of consideration one or more qualities of a complex object so as to attend to others (as when the mind considers the form of a tree by itself or the color of the leaves independently of their size or figure) **b** : the act or process of imaginatively isolating or considering apart the common properties or characteristics of distinct objects 〈~ is necessary for the classification of things into genera and species〉 **c** : the formation of a concept or an idea by such an act : the construction of a class name **3** [prob. fr. *¹abstract* + *-ion*] : the result of a mental process of abstracting : an abstract idea or a term expressing such an idea 〈his style was dense with *~s*〉; *sometimes* : a visionary or unrealistic idea **4** : inattention to present objects or surroundings : absence of mind 〈lost in ~〉 〈an air of complete ~〉 **5** : abstract quality or character 〈pantomime with a symbolic ~ that approached ballet〉 **6** *fine art* : an abstract composition or creation **7** : the merging of two or more streams into a single stream course by the deepening and widening of one valley so that it engulfs a shallower and smaller neighboring valley

ab·strac·tion·ism \-shə,nizəm\ *n* -S **1** : the creation of abstractions esp. in art **2** : the principles or ideals of abstract art

¹ab·strac·tion·ist \-sh(ə)nəst\ *n* -S **1** : one that deals with abstractions rather than with concrete things : one that takes abstractions for realities **2 a** : an abstract artist **b** : a supporter of abstractionism in art

²abstractionist \ˈ" *adj* [*abstractionist*] *fine art* : showing tendencies toward abstractionism

ab·strac·tive \(ˈ)abzˈtraktiv, əbzˈ-, -abˈst-, abˈst-, -ēv\ *adj* [ML *abstractivus*, fr. L *abstractus* + *-ivus* -ive] **1** : having the power of abstracting : of an abstracting nature 〈~ analysis〉 **2 a** : derived by a process of abstraction 〈an ~ element〉 **b** : belonging to or formed by abstraction — **ab·strac·tive·ly** *adv*

ab·stract·ly \(ˈ)•ˈ•,•\ *adv* [ME, fr. *abstract*, adj. + *-ly*] : in an abstract state or manner : SEPARATELY, ABSOLUTELY : by itself

abstract music *n* : ABSOLUTE MUSIC

ab·stract·ness *n* -ES : the quality or state of being abstract

abstract of title : a summary statement of the successive conveyances and other facts upon which a person's title to a piece of land rests

ab·strac·tor *or* **ab·stract·er** \(ˈ)•ˈ•stə(r)\ *n* -S [*³abstract* + *-or* or *-er*] : one that abstracts or makes abstracts (as of records, documents, or scientific articles): as **a** : an accounting clerk who records payroll allotments, deductions, and disbursements **b** : a person who searches out and summarizes information to be used as reference or proof in legal or insurance cases

abstract plant *n* : a comprehensive record maintained by a title-insurance company indicating liens, encumbrances, and defects affecting the title to properties located in the community where the company operates as insurer — not often in formal use

abstracts *pl of* ABSTRACT, *pres 3d sing of* ABSTRACT

ab·strac·tum \•ˈ•təm\ *n, pl* **abstrac·ta** \-tə\ [NL, fr. ML, neut. of *abstractus* abstract — more at ABSTRACT] : an abstract

ab·strict \abzˈtrikt, abˈst-, əb-\ *vt* -ED/ -ING/ -S [*¹ab-* + L *strictus*, past part. of *stringere* to draw tight — more at STRAIN] : ABJOINT

ab·strict·ed \(ˈ)•ˈ•,•\ *adj* : cut off by abstriction

ab·stric·tion \•ˈ•shən\ *n* [*¹ab-* + LL *striction-, strictio* act of pressing together, fr. L *strictus* + *-ion-, -io* -ion] : the formation of spores by the cutting off of usu. successive terminal portions of the sporophore through the growth of septa — see CONIDIUM

ab·struse \əbzˈtrüs, (ˈ)abzˌt-, əbˈst-, -abˌst-\ *adj, sometimes* -ER/ -EST [L *abstrusus* concealed, fr. past part. of *abstrudere* to push away, conceal, fr. *abs-* (var. of *ab-* ¹ab-) + *trudere* to push, thrust — more at THREAT] **1** *obs* : CONCEALED, HIDDEN 〈the eternal eye whose sight discerns *abstrusest* thoughts —John Milton〉 **2** : difficult to comprehend or understand : RECONDITE 〈the ~ calculations of mathematicians〉 〈involved and ~ language〉

ab·struse·ly *adv* : in an abstruse manner

ab·struse·ness *n* -ES : ABSTRUSITY

ab·stru·si·ty \•ˈ•səd·ē, -ətē, -i\ *n* -ES **1** : the quality or state of being abstruse 〈the intrinsic ~ of the material with which the poem grapples —J.H.Wheelock〉 **2** : something abstruse

absume *vt* -ED/ -ING/ -S [L *absumere*, fr. *ab-* ¹ab- + *sumere* to take — more at CONSUME] *obs* : to consume gradually

ab·surd \əbˈsərd, ab-, -ˈz-, -ōd\ *adj, sometimes* -ER/-EST [MF *absurde*, fr. L *absurdus* harsh-sounding, incongruous, absurd, fr. *ab-* ¹ab- + *surdus* dull-sounding, silent, deaf — more at SURD] **1** : marked by an obvious lack of reason, common sense, proportion, or accord with accepted ideas : ridiculously unreasonable, unsound, or incongruous 〈the ~ predicament of seeming to argue that virtue is highly desirable but intensely unpleasant —Walter Lippmann〉 〈don't be so ~ as to forget you're a man, and to act like a child —Anthony Trollope〉 **2** : SELF-CONTRADICTORY : fallacious by reason of contradiction **syn** see FOOLISH

ab·surd·i·ty \-dəd·ē, -ətē, -i\ *n* -ES [ME *absurdite*, fr. MF or LL; MF *absurdité*, fr. LL *absurditat-, absurditas*, fr. L *absurdus* + *-itat-, -itas* -ity] **1** : the quality or state of being absurd 〈to retain unmarred the sense of the ~ of all life —Rose Macaulay〉 **2** : something that is absurd 〈the *absurdities* of social pretense —T.S.Eliot〉 : a logical contradiction 〈a new set of inconsistencies, not to say *absurdities* —P.E.More〉

ab·surd·ly \-lē, -i\ *adv* **1** : in an absurd manner **2** : to an absurd degree 〈an ~ rich young lady〉

ab·surd·ness *n* -ES : the quality or state of being absurd

abt *abbr* about

abt system \ˈabˌt(ə)n,s-, ˈa-\ *n, usu cap A* [after Roman *Abt* †1933 Swiss railroad engineer who devised it] : a system of tracking for mountain railroads in which two or more cog-rails are used and so arranged that the teeth are not opposite on any two of the rails

ab·u·def·duf \ˌabüˈdef(ˌ)dəf\ *n, cap* [NL] : a genus of small ovate short-headed marine teleost fishes commonly found about rocks and other submerged objects and usu. included in the percoid family Pomacentridae but sometimes made the type of a separate family (Abudefdufidae)

abuild·ing \əˈbildiŋ, -ēŋ\ *adj* [*¹a-* + *building*, pres. part. of *build*] : in the process of building or of being built 〈formidable disconnents, some already strong and some ~ —*N. Y. Times*〉 〈low-cost housing now ~ at the edge of town〉

ab·u·ku·ma·lite \ˌabəˈküməˌlīt, əˈbükəmə-\ *n* -S [*Abukuma*, river on Honshu Island, Japan + E *-lite*] : a mineral $(Ca,Y)_5(P,Si)_3O_{12}(OH,F)$ consisting of a phosphate-silicate of calcium and yttrium sometimes containing uranium or thorium

abu·lia *or* **abou·lia** \(ˈ)āˈbü(y)lēə\ *n* -S [NL, fr. *²a-* + *-bulia, -boulia*] : loss of will power : abnormal lack of ability to act or to make decisions characteristic of certain psychotic and neurotic conditions — **abu·lic** *also* **abou·lic** \(ˈ)āˈb(y)ülik\ *adj*

abu·lo·ma·nia *also* **abou·lo·ma·nia** \ˌā,b(y)ülōˈmānēə\ *n* -S [NL, fr. *abulo-, aboulo-* (fr. *abulia, aboulia*) + *-mania*] : a form of mental disorder characterized by abulia

abun·dance \əˈbəndən(t)s\ *n* -S [ME *abundaunce, habundaunce*, fr. MF *abundance*, fr. *abundantia*, fr. *abundant-, abundans* + *-ia*] **1** : a great quantity or amount : large number : plentiful supply 〈an ~ of water power〉 〈illustrated with an ~ of figures and diagrams〉 — not commonly used of persons **2** : overflowing fullness : great plenty : PROFUSION 〈the ~ that pours from our factories and our farms —*New Republic*〉 〈the whole bucolic ~ of the well-kept country seat —Vicki Baum〉 **3** : plentiful supply of means or resources : AFFLUENCE, WEALTH 〈a life of ~〉 〈the economics of the new ~〉 **4** : relative quantity or amount (as with respect to an observed or supposed norm) : degree of plentifulness 〈information about the ~ of various species〉 〈measurements on meteorites also indicate very low *~s* of uranium and thorium —H.C.Urey〉 **5** *ecol* : the relative number of individuals of one kind (as of a species) in an area under consideration

abun·dant \-ənt\ *adj* [ME *abundaunt, habundaunt*, fr. MF *abundant*, fr. L *abundant-, abundans*, pres. part. of *abundare* to abound —more at ABOUND] **1 a** : possessing (as resources) in great quantity : having great plenty : RICH 〈a fair and ~ land〉 〈the promise of a more ~ life〉 **b** : amply supplied : ABOUNDING 〈~ with fly life and other natural trout food —Alexander MacDonald〉 — used with *in* and *with* **2** : more than sufficient 〈~ and well-distributed rainfall〉 : occurring or existing in great quantity : AMPLE, PLENTIFUL, COPIOUS 〈life, in all its forms, is most ~ near water —John Burroughs〉 〈her forthright manner and her ~ common sense —C.G.Bowers〉 **syn** see PLENTIFUL

abun·dant·ly \-lē, -i\ *adv* [ME *abundauntly, habundauntly*, fr. *abundaunt, habundaunt* + *-ly*] : in sufficient or more than sufficient measure : FULLY, AMPLY, PLENTIFULLY

abundant number *n* : an imperfect number that is less than the sum of all its divisors (as 12)

abundant year *n* : PERFECT YEAR

abune \əˈbün\ *chiefly Scot var of* ABOON

abu·ra \əˈb(y)ürə\ *n* -S [Yoruba *aˈbuˈraˈ*] : a medium-sized tropical African tree (*Mitragyne macrophylla*) of the family Loganiaceae having large elliptical leaves, greenish flowers, and soft wood

abu·ra·chan seed \ˌäbərəˈchän-\ *n* [Jap *abura. han*, fr. *abura* oil + *chan* pitch] : the seed of a Japanese shrub (*Benzoin praecox*) yielding an aromatic medicinal oil

abu·ra·giri \ˌäbərəˈgirē\ *n* -S [Jap *abura-kiri*, fr. *abura* oil + *kiri* paulownia] : CANDLENUT 2

aburst \əˈ-\ *adj* [*¹a-* + *burst*, v.] : BURSTING

abur·ton \əˈbərtᵊn\ *adv (or adj)* [prob. fr. *¹a-* + *burton*] : with the length athwartship (stowed the barrels and casks ~)

abus·a·ble \əˈbyüzəbəl\ *adj* [*¹abuse* + *-able*] : capable of being abused

abus·age \əˈbyüsij, -zij\ *n* -S [*²abuse* + *-age*] : improper or incorrect use of language : bad usage

¹abuse \əˈbyüz\ *vt* -ED/-ING/-S [ME *abusen*, fr. MF *abuser*, fr. *abus*, n., abuse, fr. L *abusus*, past part. of *abuti* to consume, abuse, misuse, fr. *ab-* ¹ab- + *uti* to use — more at USE] **1 a** : to attack or injure with words : reproach coarsely : DISPARAGE 〈~ a person in the most violent terms〉 **b** *obs* : to speak falsely of : MISREPRESENT 〈*abused* her to her friends〉 **2** *obs* : to cause to believe the false : lead into error : DECEIVE 〈the Moor's *abused* by some most villainous knave —Shak.〉 **3 a** : to put to a use other than the one intended : MISAPPLY 〈*abusing* the privilege by invoking it for ends not sanctioned by law —Bernard Meltzer〉 : use or apply improperly or to excess 〈farmers have learned not to ~ the soil〉 **b** : to put to a bad use : PERVERT 〈*abused* his power by profiting at the expense of others〉 : take unfair or undue advantage of 〈he has *abused* my confidence in letting this secret become known〉 **4** : to use or treat so as to injure, hurt, or damage : MALTREAT 〈~ a horse by overworking it〉 〈~ one's eyes by reading in dim light〉 : treat without consideration or fairness 〈those left behind felt themselves *abused*〉 **5 a** : MASTURBATE **b** *archaic* : to violate sexually : RAPE **c** : to commit indecent assault on — compare ²ABUSE 5

²abuse \-üs\ *n* -S [ME, fr. MF *abus*] **1** : a corrupt practice or custom : OFFENSE, FAULT 〈the buying of votes and other elections *~s*〉 **2** : improper or incorrect use : MISUSE 〈to call that state a democracy is an ~ of terms〉 : application to a wrong

〈or is it some ~, and no such thing —Shak.〉 **4** : lan
angrily 〈*bolshevist* had become . . . a vague term of ~ —
Macaulay〉 〈the political harridans would . . . attack
act of violating sexually : RAPE **b** *under some statutes*
or indecent assault not amounting to rape — compare C
ABUSE, SELF-ABUSE **6** : physically harmful treatment :
TREATMENT, ILL-USAGE 〈to be arrested for ~ of an anima
of one's health〉
SYN INVECTIVE, OBLOQUY, VITUPERATION, SCURRILITY
LINGSGATE: ABUSE, the most general word in this list of
may frequently indicate a speaker's angry intent to wou
usually suggests lack of anything that is fair or tem
〈now there is one word in the extended vocabulary of
rack-room *abuse* that cannot pass without comment . .
must not call a man a bastard unless you are prepared to
it on his front teeth —Rudyard Kipling〉 INVECTIVE may
to any denunciatory diatribe, but it often connotes a c
command of cogent language 〈John Bull stopped at no
in the way of insult; but its blazing audacity of *invective*
degenerated into dull abuse —Agnes Repplier〉 〈Cicero re
in that masterpiece of *invective* known as the Fifth Phi
—John Buchan〉 This suggestion is not necessarily presen
the rapier of sarcasm but the bludgeon of *inv*
—W.S.Maugham〉 OBLOQUY may suggest language design
shame another, language casting shame upon another
who . . . stood by me in the teeth of *obloquy*, taunt and
sneer, or insult even —Oscar Wilde〉 〈to a symbol of *ob*
to an unanswerable epithet of derogation —Bliss P
VITUPERATION suggests fluent, ready, and sustained abus
castigation nastily delivered 〈hag, nuisance, shrew, term
let loose, she assailed everybody who violated in the lea
prejudices. Presidents were nagged beyond endurance
senators, and congressmen: no one could escape the vi
her *vituperation* —F.L.Pattee〉 〈avoid reflections o
chastity of your opponent's female relations . . . Once
have gone so far it is impossible to retrace your steps and
to minor forms of *vituperation* —Robert Graves〉 SCURR
the most uncomplimentary of these words, implies meann
viciousness in attack and coarseness or foulness in lan
〈interrupted in his defense by ribaldry and *scurrility* fro
judgment seat —T.B.Macaulay〉 BILLINGSGATE may inc
very ready, easy profanity and obscenity delivered with
ticed ease 〈the *billingsgate* slang they certainly have acq
in perfection, and no white would think of competing
them in abuse or hard swearing —Sidney Baker〉 〈an a
ment of *billingsgate* that would have paralyzed a fishwife
brought blushes to a character in a Jim Tully novel or a E
O'Neill play —Herbert Asbury〉

abuse of process *law* : the malicious use of a regular ju
proceeding without probable cause

abus·er \-zə(r)\ *n* -S [ME, fr. *abusen* to abuse + *-er*]
that abuses

abusion *n* -S [ME *abusioun*, fr. MF *abusion*, fr. L *abu*
abusio, fr. *abusus* (past part. of *abuti* to misuse, abuse) +
-io -ion — more at ABUSE] *obs* : ABUSE, MISUSE; *specif* : abu
the truth : DECEPTION

abu·sive \əˈbyüsiv, -ēv *also* -üz-\ *adj* [MF *abusif*, fr.
abusivus, fr. L *abusus* + *-ivus* -ive] **1 a** : characterize
wrong or improper use or action : constituting an a
: PERVERTED 〈~ financial practices〉 **b** *archaic* : CATACH
TIC **c** *obs* : tending to deceive : FRAUDULENT, CHEATING
~ treaty —Francis Bacon〉 **2 a** : employing harsh insu
language 〈an ~ spectator〉 : characterized by or servin
abuse : SCURRILOUS 〈~ jibes〉 **b** : physically injurious
ing to damage or weaken : ROUGH 〈tools made for ~
— **abu·sive·ly** *adv* — **abu·sive·ness** *n* -ES

abus·tle \əˈ-\ *adj* [*¹a-* + *bustle*, v.] : showing great ac
: stirring busily 〈a store ~ with crowds〉

abu·u·sua \ˌabəˈsüə\ *n* -S [Ashanti] : a matrilineal exoga
clan among the Ashanti people

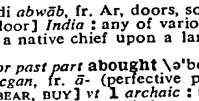
abut \əˈbət, *usu* -d·+ V\ *vb* **abutted; abutted; abutting; a**
[ME *abutten*, partly fr. OF *aboter, abouter* to touch at one
border on (fr. *a-* — fr. L *ad-* — + *bout* end, blow, fr. *b*
bouter to strike), partly fr. OF *abuter* to come to an end,
reach, fr. *a-* + *but* end, aim, purpose, of Gmc origin; ak
ON *butr* piece of wood — more at BUTT (to strike),
(end)] *vi* : to touch (as of contiguous estates) along a bord
with a projecting part 〈his land ~*s* on the road〉 : termina
a point of contact (as with an adjacent structure) : lea
rest for support (as upon another structure) — used wit
upon, or *against* ~ *vt* **1** : to border on : reach or touch
an end 〈two lots that ~ each other〉 **2** : to cause to
: support by abutment 〈~ a timber against a post〉

abu·ta \əˈb(y)üd·ə\ *n, cap* [NL, prob. fr. Sp, a plant of
genus] : a genus of tropical American woody vines (fa
Menispermaceae) — see WHITE PAREIRA, YELLOW PAREIRA

ab·uti·li \aˈbyüd·ᵊl,ī\ [NL] *adv, of an argument* : from u

abu·ti·lon \əˈbyüd·ᵊl,än, ˌabyəˈtīlən\ *n* [NL, fr. Ar *awbūt*
a plant of this genus] **1** *cap* : a large genus of mostly tro
plants (family Malvaceae) having usu. lobed leaves
solitary showy bell-shaped flowers — see FLOWERING MA
INDIAN MALLOW **2** -S : any plant of the genus *Abutilon*

abut·ment \əˈbətmənt\ *n* -S **1** : the place at which abu
occurs (at the ~ of two properties)



2 a : the part of a structure that directly receives thrust or pressure (as of an arch, vault, beam, or strut) **b** : an anchorage for the cables of a suspension bridge or aerial railway **c** : a tooth to which a denture or other prosthetic appliance is attached for support **3** : the action of abut 〈~ of two braces upon the post〉 **4** : a fixed point, surfac
body from which resistance or reaction is obtained (as
cylinder head of a steam engine or the fulcrum of a lever)

abut·tals \əˈbad·ᵊlz, -bətᵊlz\ *n pl* : the boundaries of l
with respect to other contiguous lands or highways by w
they are bounded

abut·ter \-d·ə(r), -tə-\ *n* -S : one that abuts; *specif* : the ov
of a contiguous property 〈the ~*s* on a street〉

abutting *adj* : that abuts or serves as abutment **syn**
ADJACENT

abuzz \əˈ-\ *adj* [*¹a-* + *buzz*, v.] : buzzing or filled with b
ing : filled or resounding with talk and excitement 〈Lon
was ~ over the new appointment〉

abv *abbr* above

ab·volt \ˈab,vōlt\ *n* -S [*²ab-* + *volt*] : the cgs electromagn
unit of electrical potential and electromotive force equal to
one-hundred-millionth of a volt and being the potential
ference through which transference of one abcoulomb
electricity involves a change of one erg in energy — comp
AB- table

ab·wab \abˈwäb\ *n* -S [Hindi *abwāb*, fr. Ar, doors, source
public revenue, pl. of *bāb* door] *India* : any of various fi
cesses, or imposts levied by a native chief upon a landow
or subject

aby *or* **abye** \əˈbī\ *vb, past or past part* **abought** \əˈbȯt\ [
abien, abiggen, fr. OE *ābycgan*, fr. *ā-* (perfective prefix
bycgan to buy — more at ABEAR, BUY] *vt* **1** *archaic* : to su
for or pay for (an offense) 〈lest to thy peril thou ~ it c
—Shak.〉 **2** *archaic* : to pay, suffer, or endure (as a pena
~ *vi* **1** *obs* : to pay the penalty : SUFFER **2** *obs* : END
LAST, CONTINUE 〈but naught that wanteth rest can long
—Edmund Spenser〉

abysm \əˈbizəm *also* aˈ-\ *n* -S [alter. (influenced by *abyss*)
ME *abime*, fr. OF *abisme*, modif. (influenced by words end
in *-isme* -ism) of LL *abyssus*] : ABYSS 〈the dark backward
~ of time —Shak.〉

abys·mal \-zməl\ *adj* **1** : having the characteristics of
abyss : BOTTOMLESS 〈mountain roads . . . within a few inc
of ~ precipices —W.R.Arnold〉 : immeasurably great
ENDING, PROFOUND 〈~ ignorance〉 : immeasurably low
wretched 〈~ living conditions of the poor〉 **2** : ABYS
syn see DEEP

abys·mal·ly \-zməlē, -li\ *adv* : far down in the scale of
ceptability : to an extreme degree : WRETCHEDLY, DREADFUL

Review Article

Digestive Diseases

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Therapeutic Options in Patients with Barrett's Esophagus

Kie N. Lim Patrick J. Waring Roxan Saidi

Division of Digestive Disease, Emory University School of Medicine, Atlanta, Ga., USA

Key Words
Barrett's esophagus · Intestinal metaplasia · Ablation therapy

Abstract
The rising incidence of esophageal adenocarcinoma has focused attention on the only known risk factor: Barrett's esophagus. Practice guidelines for the diagnosis, surveillance and management of Barrett's esophagus were published recently. Although the ultimate goal in the management of this premalignant condition would be the permanent elimination of Barrett's mucosa, current therapeutic options are limited or still in the investigational stages. This review summarizes current medical and surgical treatment options and introduces endoscopic ablative modalities currently under investigation.

Introduction

Over the past three decades, a striking threefold rise in the incidence of esophageal adenocarcinoma [1, 2] has focused attention on the only established precursor lesion: Barrett's esophagus. This attention has resulted in refinement of the diagnosis of Barrett's, and better, but still incomplete, understanding of the natural history of the metaplasia-dysplasia sequence in Barrett's epithelium. In addition, certain epidemiologic characteristics of the population at risk for this premalignant condition are coming to light [3].

The diagnosis of Barrett's esophagus is now made when any length of columnar-lined epithelium (CLE) with intestinal metaplasia (IM) is present in the tubular esophagus [4]. Because this diagnosis is stricter in one aspect (the presence of IM and not simply columnar metaplastic cells) and looser in another (any length of CLE rather than CLE ≥ 3 cm) when compared to previous definitions, the incidence, prevalence and risk of dysplasia development must be reassessed.

A recent review of the epidemiology of the columnar-lined esophagus by Cameron [5] described a 3–5% prevalence of CLE in patients with reflux symptoms and a 1% prevalence of Barrett's esophagus in all patients undergoing upper endoscopy for any clinical indication. Studies using the newer diagnostic criteria estimate the prevalence of Barrett's at 12% for reflux patients in the community [3] and up to 48% for selected patient groups (Caucasians with reflux at a referral center) [6]. However, prospective population studies based on these new criteria are needed to determine the natural history and risk of dypslasia in CLE with IM of <3 cm or IM at the gastroesophageal junction.

Due to the potentially significant number of reflux patients at risk for Barrett's esophagus, the American College of Gastroenterology has proposed practice guidelines for endoscopic screening and subsequent surveillance based on the presence and grade of dysplasia [7]. Treatment recommendations in these guidelines offer

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Kie N. Lim, MD
Division of Digestive Diseases
Emory University School of Medicine
1639 Pierce Drive, WMB 2101, Atlanta, GA 30322 (USA)
Tel. + 1 404 727 5638, Fax + 1 404 727 5767

Table 1. Management strategies for Barrett's esophagus: treatment options

Acid suppression in symptomatic patients
Reflux control with antireflux surgery in symptomatic patients
Endoscopic ablation of Barrett's mucosa
Surgical resection of high-grade dysplasia
Combination therapy

antireflux therapy (medical or surgical) in patients with reflux symptoms and Barrett's esophagus with no or low-grade dysplasia, and advise esophagectomy versus continued surveillance in patients with high-grade dysplasia (HGD).

Recently, however, a new treatment modality, endoscopic ablation, has been developed which may cause regression or halt the progression of the metaplasia-dysplasia sequence in Barrett's esophagus. This review summarizes the effectiveness of current medical and surgical options (table 1) and introduces the endoscopic ablative methods currently under investigation.

Medical Treatment

The medical management of Barrett's esophagus is controversial and has been aimed at controlling the reflux of acid into the esophagus. This can be achieved by using proton pump inhibitors or histamine-receptor antagonists to control symptoms and heal esophagitis. However, symptom control per se does not correlate with adequate control of acid reflux by esophageal pH monitoring in patients with or without Barrett's esophagus [8].

Multiple studies have demonstrated that acid suppression which effectively controls symptoms can lead to the appearance of squamous islands within columnar-lined epithelium but does not cause regression of Barrett's, i.e. a decrease in the overall length [9, 10]. Recent studies show that further escalation in drug doses, to achieve normal esophageal pH, does not seem to result in regression either. Of 27 patients with Barrett's esophagus on 60 mg of Lansoprazole for symptom control, 13 agreed to undergo ambulatory 24-hour pH monitoring while on therapy. Eight of the 13 patients had normalization of their esophageal pH, improvement in symptoms, and healing of esophagitis. Despite an increase in the number of squamous islands, the length of Barrett's esophagus did not change after an average of 5.7 years follow-up [11]. This suggests that metaplasia itself may not be reversible or that elements other than acid may play a role in the development and maintenance of columnar metaplasia.

Furthermore, many patients with Barrett's esophagus may be found incidentally and have no symptoms of reflux to guide pharmacotherapy. Although the degree of acid reflux in patients with Barrett's rivals that of patients with esophagitis [12], the use of acid-suppressive medications in asymptomatic refluxers with Barrett's esophagus cannot be recommended at present. Since there are sparse data demonstrating either regression of Barrett's esophagus or a reduction in the risk of progression to dysplasia, the role of acid suppression in Barrett's should be symptom-based [7].

Surgical Management of Barrett's Esophagus

Antireflux Surgery

The current indication for antireflux surgery is to provide long-term control of reflux symptoms. Its effectiveness in reducing acid in the esophagus is equivalent to acid-suppressive medications. Although it offers the added physiologic benefit of reducing esophageal exposure to the nonacid components of gastric refluxate, antireflux surgery has not been shown to cause regression of Barrett's. However, some studies suggest that it may play a role in altering or delaying the malignant progression of Barrett's.

In the only prospective study randomizing patients to medical vs. surgical therapy to date, after a median follow-up of 4.5 years, of 32 patients with Barrett's without dysplasia who received standard medical treatment or failed antireflux surgery, 7 showed dyplastic changes including 2 patients with severe dysplasia. The 27 patients who had successful and effective antireflux surgery (by clinical and pH criteria) did not develop any grade of dysplasia. It was also observed that the median length of the Barrett's mucosa was noted to decrease from 5 to 4.5 cm in the surgical group and increased from 4 to 5 cm in the medically treated group ($p < 0.01$) [13]. However, this observation questions the clinical relevance and generalizability of change in length of Barrett's as a parameter of regression in clinical trials, particularly in light of the finding of Kim et al [14] that approximately 10% of patients had a change of ≥ 4 cm in the lower esophageal sphincter level on endoscopy and manometry between examinations.

Another prospective but nonrandomized study of Barrett's patients (presence of dysplasia on enrollment was

not stated) undergoing antireflux surgery found that esophageal cancer occurred only in the early postoperative years (longest screening time to finding cancer was 3.25 years) and not randomly over the follow-up years (median of 6.5 years, maximum of 18.2 years) [15]. This suggests that antireflux surgery may prevent the progression of Barrett's metaplasia to dysplasia. However, the impact of surgery on the progression of dysplasia to cancer cannot be determined from these data since the cancers may have been present preoperatively and the period of such progression may exceed 18 years.

Overall, the data from surgical series support the inference from trials of medical acid suppression that reflux may not be the pivotal factor in the maintenance or progression of Barrett's. Neither medical nor surgical control of acid reflux effectively induces the regression of Barrett's when assessed by a decrease in the length (or surface area) of CLE. But since different substances in the refluxate may be involved in the initial rather than the subsequent metaplastic-dysplastic mutagenic sequence, antireflux surgery may arrest the progression of Barrett's [16].

Esophagectomy

Until recently, esophagectomy has been the standard of therapy for patients with Barrett's epithelium containing HGD or carcinoma in situ. This approach is based on surgical data demonstrating that esophagectomy specimens harbored unsuspected foci of cancer and even lymph node involvement in approximately 50% of patients with HGD [17–20]. In nonsurgical series, patients with HGD referred for esophagectomy from Barrett's surveillance programs had earlier stage tumors and better outcomes than nonsurveyed patients, and the prevalence of unsuspected adenocarcinoma was approximately 20% [21].

New information about the natural history of Barrett's suggests that the progression from HGD to cancer may take over 5 years. A recent abstract reported that 43 of 58 patients (74%) with HGD remained status quo histologically or regressed to less severe histology after a mean follow-up of 10 years [22]. The remaining 15 patients (26%) progressed to intra- or submucosal cancer. Another prospective series described 42 HGD patients under biopsy surveillance every 3–6 months. Although adenocarcinoma was detected in 8 patients as early as 9 months after HGD was found, the remaining 34 patients did not progress to adenocarcinoma over a mean follow-up of 7.5 years [23].

These insights into the HGD to cancer sequence from surveillance studies suggest that in patients with HGD and synchronous foci of cancer (usually detected within 1 year), esophagectomy is the treatment of choice. However, for a significant number of HGD patients who have no cancer detected for several years during close biopsy surveillance, or who have severe comorbidities, nonsurgical ablation may be a treatment option.

Endoscopic Ablation of Barrett's Esophagus

One of the many new technical developments in endoscopy is ablative therapy. This form of minimally invasive destruction of mucosal lesions, benign or malignant, rests on the principle that the epithelium of the intestinal tract regenerates normally after injury. Furthermore, targeted injury of the luminal mucosa would presumably limit the risks of submucosal damage such as stricturing or perforation. Thus, this novel approach opens a new therapeutic option for Barrett's which, in contrast to medical or surgical therapy, can potentially induce the regression of Barrett's epithelium, prevent the progression of dysplasia and allow the regeneration of normal squamous mucosa in its usual milieu.

Current endoscopic ablative techniques under development include thermal, photochemical, ultrasonic and cryothermal methods and the experience to date is summarized below. Although each is technically feasible, the optimal parameters for ensuring complete ablation and minimizing complications in a practical manner are the subject of investigation at this time. Once these are determined and Barrett's epithelium or dysplasia can be effectively eliminated, antireflux surgery must be considered to prevent recurrence in the long term. It must be noted that all ablative treatments are carried out in conjunction with proton pump inhibition of gastric acid production or, more recently, antireflux surgery.

Electrocautery and Laser (Thermal Ablation)

Multipolar electrocoagulation (MPEC) to ablate Barrett's epithelium has been described in several small series. Sampliner et al. [24] documented complete reversal and regression of Barrett's epithelium with a mean length of 4.7 cm in 12 patients after an average of 6–7 sessions of MPEC. Follow-up for an average of 12 months showed no histologic or endoscopic recurrence in 10 patients [24]. Similarly, another study showed that 90% of the 21 study patients had complete elimination of the targeted Barrett's mucosa 1year after treatment with MPEC. Multiple

sessions were also required, the number depending on the length of the Barrett's segment (average of 3.4 sessions for Barrett's of >2 cm in length) [25]. Furthermore, this is a contact method requiring direct apposition of probe and mucosa for delivery of energy, hence, with in vivo variations of peristalsis, respiration, and insufflation, a variable depth of injury is seen and may lead to undertreatment (and residual subsquamous columnar cells) or overtreatment (and perforation or stricturing). The former has been reported in several cases of Barrett's ablation therapy, regardless of energy form. But the latter complications have not been reported with MPEC [24, 26]. The practical advantages of this method are the low cost of utilization, its widespread availability, and the familiarity of most endoscopists with the MPEC technique.

Attempts to thermally ablate Barrett's mucosa with different lasers (KTP, argon and Nd:YAG) have also been investigated. The KTP laser has several advantages over other types of lasers; it offers superficial coagulation and variable depth effect when the pulse duration is adjusted and, furthermore, is a noncontact technique which allows a free-hand, paintbrush-like manner. Two studies using KTP ablation, one in 16 patients without dysplasia [25] and another in 10 patients with dysplasia or early adenocarcinoma [27], demonstrated that squamous regeneration is possible but complete reversal of Barrett's (endoscopic and histologic) was achieved in only 12.5 and 80% of patients respectively, due to persistence of residual subsquamous intestinal metaplasia. The variability in response is attributable to differences in power settings, session frequency and intensity of proton pump inhibition between the two trials.

Similar data exist for other types of lasers including the argon laser and Nd:YAG laser [28–31]. For example, in one series, 10 patients underwent ablation of only half of the circumference of their Barrett's (average of 3 sessions) with an argon laser while on acid suppression medication. Areas that were ablated showed partial or complete regeneration of squamous mucosa that was not observed in control nonablated locations. Follow-up ranged from 6 to 38 weeks [28]. Laser ablation with noncontact Nd:YAG is limited to a case report [29] and a small randomized trial with 4 patients in each arm which showed no difference in the Barrett's length 6 months after ablation [30].

In a novel and rational approach, a Finnish group performed contact Nd:YAG ablation of Barrett's after antireflux surgery, thus ensuring the absence of any injurious refluxate in the healing esophagus. Eleven of 17 postsurgical patients who agreed to participate underwent a mean of 4 treatments 3 months apart. Although 2 of the 11 had residual intestinal metaplasia at the gastric cardia, none was detected over the next 2 years in the remaining patients. As expected, there was no change in the length of Barrett's in the control group who had refused ablation.

Argon Plasma Coagulation

Argon plasma coagulation (APC) is a technique that delivers controlled monopolar electrocoagulation via a stream of ionized argon gas ignited by a high voltage discharged at the tip of a specialized flexible probe. It is a noncontact ablative method with a predetermined depth of injury (approximately 2 mm) that is most often used for coagulation of bleeding surface lesions such as arteriovenous malformations.

Many studies of APC ablation in Barrett's were reported in 1998. Each has demonstrated variable success in the sustained restoration of normal squamous epithelium in Barrett's. In one study 15 of 21 patients (70%) with Barrett's mucosa without dysplasia had normal mucosa restored 8 months after ablation with APC [32]. In another study, of 25 patients with Barrett's esophagus without HGD who underwent ablative therapy with APC, 15 patients (60%) had some response but only 8 patients (32%) achieved complete endoscopic and histologic restoration and 2 patients (8%) had no response at all [33]. Another small study confirmed the above findings where 3 of the 8 study patients still had intestinal metaplasia by biopsy after therapy was completed [32].

In the largest APC ablation study to date, 30 patients (4 low-grade dysplasia, 3 HGD) with Barrett's of >3 (median 5, range 3–17) cm were treated [35]. Successful response was defined as residual CLE of <2 cm. All 27 patients who completed treatment had a macroscopically successful response over a median follow-up of 9 months including 2 patients with HGD who had both endoscopic and histologic return to squamous epithelium at 1 year. The restoration of squamous epithelium in 4 patients with persistent reflux symptoms was only achieved after doubling the omeprazole dose to 40 mg/day.

However, as in the previously cited studies, a significant 30% of patients continued to have subsquamous intestinal metaplasia. Whether these residual areas of Barrett's have the same risk of progression to dysplasia postablation is not clear and, therefore, continued biopsy surveillance of all ablated segments is mandatory. This study also reports the first instance in any Barrett's ablation experience of perforation and subsequent death, both occurring relatively early in the trial. These types of complications,

undertreatment with residual Barrett's and overtreatment with resultant perforation or possibly stricturing, underscore the technical challenges of endoscopic thermal ablation in terms of depth of injury and operative skill.

Photodynamic Therapy

Photodynamic therapy (PDT) has received much attention and holds much promise as a therapeutic option in patients with HGD and early esophageal cancer. This form of noncontact nonthermal ablative therapy involves the in situ photoactivation of an otherwise nontoxic drug, a photosensitizer, which has accumulated in tumor and normal tissues following oral or intravenous administration. The photosensitizer is activated by a wavelength of light that matches the absorption spectrum of the drug. The resultant photochemical reaction gives rise to highly active singlet oxygen species capable of causing cell death directly and a necroinflammatory cascade indirectly. Ideally, this effect selectively destroys only abnormal cells because the photosensitizer accumulates preferentially in the dysplastic or neoplastic cells and because only the target mucosa is illuminated during a treatment session.

Currently, in the USA, the only approved sensitizer is porfimer sodium (Photofrin®), a hematoporphyrin derivative, for the palliation of obstructive esophageal cancer. The technique of PDT for this indication involves administration of porfimer sodium intravenously followed by delivery of 630 nm light generated by a laser 48 h later using a cylindrical diffuser or a windowed centering esophageal balloon. The same technique is used for treating Barrett's esophagus, but may vary slightly with other photosensitizers. There is a 4- to 6-week period of skin photosensitivity after Photofrin® adminstration.

For the palliation of obstructive esophageal cancer, the effectiveness of PDT equals that of Nd:YAG laser therapy [36]; but there is hope for its application n HGD and intramucosal carcinoma as a curative ablative modality due to an approximate depth of injury of 3 mm. The first encouraging results were reported in 1995 in 123 nonsurgical candidates with early squamous or adenocarcinoma of the esophagus [37]. PDT achieved a high rate of complete tumor response at 6 months (87%) in small (0.5–4 cm in diameter and T1 or T2 stage) esophageal tumors. Recurrences detected at a superficial stage after complete initial destruction responded to additional PDT.

Based on these promising results in early esophageal cancers, Overholt et al. [38, 39] used Photofrin PDT in 100 patients with Barrett's esophagus with dysplasia or superficial cancer (T1 or T2). During a follow-up of 4–84 (mean 19) months, Nd:YAG laser ablation was also performed in 84 patients to destroy small residual areas of Barrett's mucosa and omeprazole 20 mg b.i.d was given. Barrett's was completely eliminated by biopsy in 43% of patients (including 4 or 12 patients with T1 adenocarcinoma). Dysplasia was cleared in 78 of the 100 patients, and 10 of the 13 superficial cancers were eliminated. Those with persistent dysplasia (9%) either remained status quo or had a regression in their dysplasia grade.

Although no perforations occurred, these impressive responses were accompanied by esophageal strictures in 34% of patients as well as moderate chest pain and dysphagia requiring intravenous fluids in most. Of special concern is the development of dysplasia in segments of Barrett's not treated with PDT and the progression of subsquamous Barrett's to HGD or cancer in 3 patients at 6, 18 and 22 months after PDT.

Recent studies with a newer photosensitizing agent, 5-aminolaevulinic acid (ALA), appeared to show similar responses with better tolerance, lesser complications and several advantages [40, 41]. First, ALA is more rapidly eliminated from the body and hence decreases the duration of photosensitivity from several weeks to a couple of days. Second, it accumulates preferentially in the mucosa and not in submucosa. This offers more selective superficial damage limiting the risk of strictures and perforation. Third, ALA may have more tumor selectivity [40] and finally, it can be given orally.

In the largest series to date, Gossner et al. [42] treated 32 nonsurgical candidates with HGD ($n = 10$) or mucosal cancer ($n = 22$) using ALA as the photosensitizer in PDT. Histologic eradication was achieved in all HGD as well as adenocarcinomas of < 2 mm thickness [42]. Far fewer complications were noted than with porfimer sodium; no stricturing was induced because the depth of injury is limited to the mucosa and the photodynamic inflammatory cascade does not affect the submucosa. The only complications mentioned in this study were transient nausea and asymptomatic mild transaminases elevations. Since the follow-up was limited (ranging from 1 to 30, mean of 9.9 months), the durability of the ablation is unknown. However, 2 cases of subsquamous columnar islands were noted on follow-up.

The advent of PDT has demonstrated the feasibility of ablating dysplastic mucosa and even early cancers of the esophagus in a more complete manner than thermal or APC ablation. This technique will be further refined by improving the precision and uniformity of light delivery to targeted areas and by the development of more tissue selective and specific photosensitizers with reduced photosensitivity periods.

Ultrasonic Energy

This mechanical ablative method utilizes ultrasonic energy to injure epithelial cells without damaging muscle or stromal cells. In the only study to date, a Cavitron Ultrasonic Surgical Aspirator, was placed directly on the esophageal mucosa of pigs through a standard percutaneous gastrostomy. Ultrasonic energy was delivered to the circumference of the esophagus and the ablated tissue aspirated for cytologic analysis [43]. Complete ablation of epithelium superficial to the muscularis mucosa was achieved in one session without stricture formation. The current limitation of this technique is that the ultrasonic energy must be delivered through a rigid system, thus, its practical role in ablating Barrett's epithelium may be limited to application during antireflux surgery.

Cryotherapy

Cryotherapy has been used to ablate tissues in solid organs such as the liver, but new flexible delivery systems have allowed endoscopic experimentation in hollow organs. A catheter spray system to deliver liquid nitrogen was used in an animal model to freeze the esophageal epithelium and resulted in targeted cell death by formation of ice crystals intra- or extracellularly. Cellular damage can either be caused indirectly as a result of osmotic shifts between tissue compartments, or directly by mechanical damage from ice crystals. However, because the degree and depth of mucosal damage could not be adequately controlled in this pilot study, one stricture and one perforation occurred in the 16 animals [44]. Pilot clinical trials are underway.

Summary of Ablative Methods

Endoscopic ablative therapy appears to be a promising, feasible and novel approach to treatment of Barrett's esophagus. Until efficacy and effectiveness have been demonstrated, this therapy is most appropriately performed in a research setting for patients with HGD or early superficial cancer who are not surgical candidates. It is minimally invasive, superficial and carries less morbidity than surgery, but has the potential to cure a patient with mucosal neoplasia of the esophagus. For patients with low-grade or no dysplasia and operable patients with HGD, at this time, ablative therapy can only be undertaken in clinical trials with the understanding that although current ablative modalities appear to cause regression, their impact on the risks of progression are unknown.

Several issues still need to be addressed concerning the use of any ablative method. At the forefront are technical issues regarding the optimal depth of injury, the controlled and uniform delivery of the ablative energy, and the ease and cost of its delivery. These factors will determine the efficacy of endoscopic ablation in terms of its completeness and durability. Until a form of ablative therapy is shown to restore normal squamous epithelium in the entire segment of Barrett's without residual submucosal columnar islands, assessing the completeness of ablation will entail continued endoscopic biopsy surveillance for an indefinite period. This surveillance will be complicated by the absence of endoscopically recognizable features of Barrett's.

Furthermore, given the long natural history of Barrett's development, measuring the durability of ablative therapy will be difficult and probably dependent on the effectiveness of antireflux measures. It can be argued that ablative therapy for Barrett's should always be followed by antireflux surgery for definitive management.

Table 2. Management strategies for Barrett's esophagus in 1999 based without dysplasia status

Barrett's without dysplasia
Symptom control[1] and surveillance biopsies
Low-grade dysplasia
Symptom control[1] and surveillance biopsies
Endoscopic ablation, antireflux surgery, surveillance biopsies[2]
High-grade dysplasia/adenocarcinoma confined to mucosal (stage T1)
Esophagectomy
Endoscopic ablation, antireflux surgery, surveillance biopsies in the nonsurgical candidate[2]

[1] Medical or surgical.
[2] In research trials only.

Conclusion

In summary, although a number of ablative treatment options for Barrett's esophagus have appeared, the long-term effectiveness of these modalities and the unclear natural history of this condition precludes the recommendation of any one specific treatment modality. Until we can clearly define the subgroup of patients who possess the definite risk of malignant progression, choosing any one ablative option will require investigation and careful weighing of risks and benefits based on a patient's dysplasia status (table 2). The risk of undertreatment and possible subepithelial progression to cancer beyond a curative window must be balanced against overtreatment and sub-

Table 3. Comparison of current treatment modalities for Barrett's esophagus

Treatment	Availability	Advantages	Disadvantages	Outcome
Medical treatment	Widespread	Noninvasive	Ineffective pH control in many patients	Squamous islands, no regression
Antireflux surgery	Widespread	Possible to reduce risk of malignancy	Morbidity and mortality	Squamous islands, no regression
Esophagectomy	Widespread	Remove source of malignant potential	Morbidity and mortality	Favorable in early cancer (cure)
Ablative treatment				
MPEC	Widespread	Common technique, no reported complications	Contact therapy, multiple sessions, variable injury	Complete regression with subsquamous islands
LASER	Limited	Common, noncontact, no reported complications	Variable injury, multiple sessions	Complete regression with subsquamous islands
APC	Some centers	Noncontact, technically simple	Variable injury, multiple sessions	Complete regression with subsquamous islands
PDT	Limited	2 sessions per treatment	Photosensitivity and stricturing	Favorable in early cancer
Ultrasonic treatment (animal)	Very limited	One session per treatment	Rigid instrument, operative procedure	Complete regression
Cryotherapy (animal)	Very limited	Noncontact	Variable injury	Unclear

jecting patients to unnecessary and potentially dangerous treatments. Development of specific biological markers that can predate malignant changes in Barrett's [43], and the more sensitive endoscopic assessment of Barrett's mucosa with techniques such as light-induced fluorescence endoscopy [46, 47] should improve the stratification of treatment options. In the meantime, the management of patients with Barrett's esophagus can be based on a combination of symptom control and appropriate referral to research centers for trials of endoscopic ablation (table 3).

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